Does maternal lamotrigine use increase the risk for club foot?

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Rationale: In an exploratory analysis of the EUROCAT Antiepileptic Database, we found an association between lamotrigine (**Fig. 1**) monotherapy in the first trimester of pregnancy and club foot (**Fig. 2**) **[1]** based on five cases where 1.8 were expected ($p<0.05$). We investigated whether there was independent evidence of a continuing association between lamotrigine monotherapy and club foot in subsequent registrations in the database, which would suggest it was not a chance finding.

Fig. 1 Lamotrigine

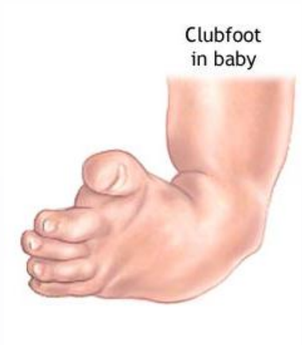

Fig. 2 Image of a club foot in a baby

Methods: The study population of this independent dataset covered 757,797 births from 16 EUROCAT registries (**Fig. 3**), born 2003-2008, including 19,358 malformed livebirths, stillbirths and terminations of pregnancy following prenatal diagnosis. Cases of club foot excluded cases associated with spina bifida. We calculated the proportion of club foot among non-chromosomal malformed pregnancy outcomes exposed to lamotrigine (*n*= 20) and compared this with the proportion of club foot among non-chromosomal malformed outcomes not exposed to any antiepileptic drug (AED) (*n*= 17,897). We also compared this with the proportion of club foot among non-chromosomal malformed pregnancy outcomes exposed to other AEDs (*n*=450) in the entire dataset (1995-2008, 4,636,825 births).

Results: We found 3 cases of club foot among 20 lamotrigine monotherapy-exposed registrations instead of the expected 1.08 ($p<0.05$) based on the non-exposed proportion of clubfoot of 4.5%. Of the total of 8 club foot cases reported to date (old and new data), 7 were isolated and 5 were bilateral (1 laterality unknown). The proportion of club foot among pregnancy outcomes exposed to other AEDs was 4.2% in the entire dataset.

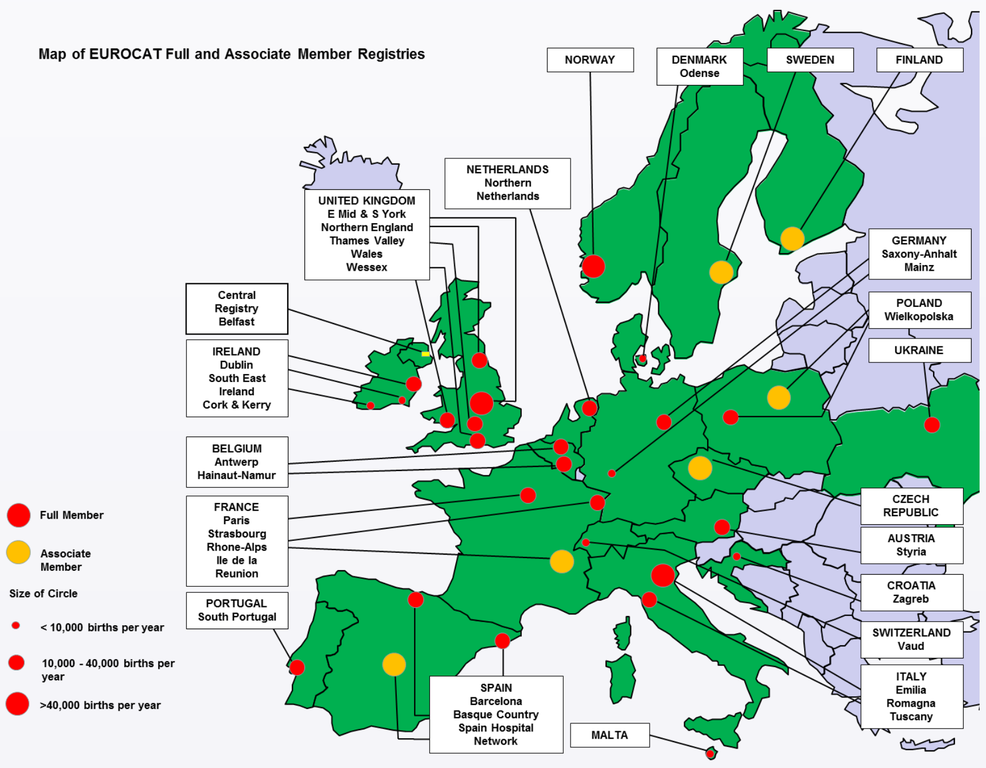

Fig. 3 EUROCAT Full and Associate Member Registries

Conclusion: We tested the signal of an association between lamotrigine and club foot in an independent dataset and found it again statistically significant. We also found it to be specific for lamotrigine, and not for other AEDs tested. Club foot is a complex anomaly, related to various genetic and environmental factors. This indication should be interpreted with caution. We will continue to monitor with EUROCAT data and invite responses to this signal from existing cohort studies.

References

[1] Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LTW and the EUROCAT Antiepileptic Drug Working Group (2008), Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? *Neurology,* 71, 714-722

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